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09/763,362	04/23/2001	Kazuma Tomizuka	081356/0158	4670

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EXAMINER	
TON, THAIAN N	
ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/763,362	Applicant(s) TOMIZUKA ET AL.	
	Examiner Thaian N. Ton	Art Unit 1632	

-- The MAILING DATE of this communication appears n the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-92* is/are pending in the application.

4a) Of the above claim(s) *26-83 and 85* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25,84 and 86-92* is/are rejected.

7)☒ Claim(s) *14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' Preliminary Amendment, filed 4/23/01, Paper No. 3, has been entered.

Claims 1-92 are pending. Claims 1-25, 84 and 86-92 are under current examination.

Election/Restrictions

Applicant's election with traverse of Group I in Paper No. 8 is acknowledged. The traversal is on the ground(s) that Group V [claims 86-92] should be examined with Group I [claims 1-25] because Group I recites the use of a product [a targeting vector] and Group V recites the product [the targeting vector]. As stated by Applicants, 37 CFR 1.475(b)(2) states that a national stage application containing claims to different categories of invention will considered to have unity of invention if the claims are drawn to a product and process of use of said product. Applicants' arguments are found persuasive and Groups I and V will be examined together. Accordingly, claims 1-25, 84 and 86-92 are under current examination.

Claims 26-83 and 85 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected groups(s), there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8.

Claim Objections

Claim 14 objected to because of the following informalities: the term plurality is mis-spelled. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-25, 84 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for producing a mouse ES cell comprising a modified foreign chromosome or fragments thereof and mouse ES cells comprising a recombinant chromosome or fragment thereof, does not reasonably provide enablement for methods for producing cells, for the breadth claimed, comprising modified foreign chromosomes or fragments thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claimed invention is directed to methods for producing a cell comprising a modified foreign chromosome or a fragment thereof, comprising preparing a microcell comprising a foreign chromosome or a fragment thereof, and transferring said foreign chromosome or a fragment thereof into a cell with high homologous recombination efficiency through its fusion with said microcell, in said cell with

high homologous recombination efficiency, inserting a targeting vector by homolgous recombination into a desired site of said foreign chromosome or fragment thereof and a desired site of a chromosome derived from said cell with high homologous recombination efficiency, thereby marking the desired site; and causing the deletion and/or translocation to occur at the marked site of the foreign chromosome or fragment thereof.

The claimed invention is directed to cells that comprise modified foreign chromosomes or fragments thereof. In further embodiments, the claims are limited to ES cells [see claim 19]. As such, the claimed invention, as broadly written, encompasses embryonic stem cells. However, the state of the art is such that ES cell technology is generally limited to the mouse system at present, and that only "putative" ES cells exist for other species (see Moreadith *et al.*, **J. Mol. Med.**, 1997, p. 214, S*ummary*). Note that "putative" ES cells lack a demonstration of the cell to give rise to germline tissue or the whole animal, a demonstration which is an art-recognized property of ES cells. Moreadith *et al.* supports this observation as they discuss the historical perspective of mouse ES cells as follows:

"The stage was set-one could grow normal, diploid ES cells in culture for multiple passages without loss of the ability to contribute to normal development. Furthermore, the cells contributed to the development of gametes at a high frequency (germline competence) and the haploid genomes of these cells were

transmitted to the next generation. Thus, the introduction of mutations in these cells offered the possibility of producing mice with a predetermined genotype."

Such a demonstration has not been provided by the specification or the prior or post-filing art with regard to the generation of any species of animal ES cells, other than the mouse, which can give rise to the germline tissue of a developing animal. In addition, prior to the time of filing, Mullins *et al.* (**Journal of Clinical Investigation**, 1996) report that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated." (page 1558, column 2, first paragraph). As the claims are drawn to methods involving the manipulation of animal embryonic stem (ES), the state of the art supports that only **mouse ES cells** were available.

This is further supported by Pera *et al.* [**Journal of Cell Science** 113: 5-10 (2000)] who present the generic criteria for pluripotent ES or EG cells [see p. 6, 2nd column] and state that, "Thus far, only mouse EG or ES cells meet these generic criteria. Primate ES cells meet the first three of the four criteria, but not the last. Numerous other candidate mammalian ES cells have been described over the years in domestic and laboratory species, but only in the mouse have all criteria been met rigorously." [See p. 6, 2nd column, last paragraph].

Accordingly, in view of the state of the art of ES cells, and the lack of guidance or teachings provided by the specification for the availability of ES cells

from species other than mouse, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1, as written is unclear. The claim recites "transferring said foreign chromosome into a cell with high homologous recombination efficiency through its fusion with said cell" in part (a) of the claim. It is unclear because the claim as written, implies that the cell has high homologous recombination efficiency because of fusion of the chromosome or fragment (s). Furthermore, it is unclear if the "transferring" step described is through fusion of the microcell to the cell with high homologous recombination. The claim is further unclear because in part (b) of the claim, "and/or" is recited. It is unclear if this term is meant to be further limiting "and" or in the alternative "or". Part (b) of the claim recites, "derived from", it is unclear what the metes and bounds of "derived from" are, as the term is not clearly defined by the claim. Part (b) of the claim is further unclear, because it recites, "marking" the desired site. It is unclear how inserting a targeting vector into a desired site of the foreign chromosome "marks" a desired site. Part (c) recites "and/or", and it is unclear if this term is meant to be further limiting "and", or in the alternative "or". Part (c) is unclear because it recites "causing" deletion and/or

translocation to occur. "Causing" is not defined by the claim. Clarification and/or amendment is requested. Claims 2-25 depend from claim 1.

Claim 2, is unclear because it recites that a plurality of the cells with high homologous recombination efficiency are subjected to whole cell fusion after steps (a) and (b). However, in step (a) there is a fusion step. As such, it is unclear if there is a second fusion step. Claims 3 and 8 depend from claim 2.

Claim 10 recites the term "and/or". It is unclear if this term is meant to be further limiting "and" or in the alternative "or". Claims 11-16 depend from claim 10.

Claim 16, as written, is unclear. The claim recites the terms "derived from" in line 3 of the claim. It is unclear what the metes and bounds of this term are as the claim does not particularly define how the chromosomes are "derived from" a cell with high homologous recombination efficiency.

Claim 19, as written, is confusing. The claim recites, "an embryonic stem cell (or ES cell)." It is suggested that the claim be written (ES cell) for clarity.

Claim 24, as written, is unclear. The claim recites that the green fluorescent protein encoding gene is "derived from". It is unclear what the metes and bounds of "derived from" are.

Claim 25, as written, is unclear. The claim recites that the foreign chromosome is derived from a human. It is unclear what the metes and bounds of the term "derived from" are.

Claim 84, as written, is unclear. The claim recites the term "and/or" in lines 2, 6. It is unclear if this term is meant to be further limiting "and" or in the alternative "or".

Claim 86, as written, is unclear. The claim recites the term, "derived from" in line 2 of the claim. This term is unclear because the metes and bounds of the term are not clearly defined. How is the centromere sequence "derived"? Claim 87 depends from claim 86.

Claim 88, as written, is unclear. The claim recites the term "and/or" in line 2 and 4 of the claim. It is unclear if this term is meant to be further limiting "and" or in the alternative "or". Claims 89-92 depend from claim 88.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-19, 21-23, 25, 84, 86-92 are rejected under 35 U.S.C. 102(b) as being anticipated by Tomizuka *et al.* [**Nat. Gen.**, 16:133-143, 1997].

Tomizuka teach the introduction of human chromosome or chromosome fragments into mouse ES cells by microcell-mediated chromosome transfer [MMCT]. In particular, Tomizuka teach the introduction of chromosomes (or chromosome

derived fragments) which carry the genes for human antibodies from unrearranged human Ig genes [Ig heavy, λ or κ genes], which are found on human chromosomes 2, 14 and 22, into mouse ES cells. In particular, whole cell fusion of human primary fibroblasts with mouse A9 ES cells was performed, and the resulting hybrid cells were screened by PCR and FISH [see p. 133-134 and Figure 1]. Cells were selected by G418 or puromycin drug resistance [see p. 134, col 1-2, bridging paragraph]. It was found that intact human chromosomes 14 and 22 were identified in hybrids A9/14-C11 and A9/22-G2. These cells were then injected into 8-cell stage embryos and produced chimeric mice [see p. 137, 2nd column]. Tomizuka state that this demonstration would allow for the generation of mice containing any desired human chromosome or fragments derived from a specific chromosomal region [see p. 140, col. 1, 2nd paragraph, lines 7-14]. Tomizuka teach using the Cre-loxP system to replace specific mouse chromosomal regions with the corresponding human chromosomal fragment in the microcell-hybrid ES cells by homologous recombination [see p. 140, 2nd column, 2nd full paragraph, lines 4-7].

Note that Tomizuka teach the limitation of the claims with regard to a targeting vector containing a "telomere sequence" [*e.g.*, claim 7] because they teach that intact human chromosomes were identified in the microcell-hybrid ES cells, and intact human chromosomes would have a telomere sequence.

Accordingly, Tomizuka *et al.* anticipate the claimed invention.

Claims 1-6, 19, 21-23, 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Kuncherlapati *et al.* [**WO 94/02602**, 3 February 1994].

Kuncherlapati *et al.* teach a method of producing mouse ES cells which have nonfunctional endogenous immunoglobulin genes, and have been introduced with xenogeneic, e.g., human heavy and light chain immunoglobulin genes [see p. 10, lines 27-37 and p. 11, lines 1-16]. In particular, they teach that a yeast artificial chromosome [YAC] can be introduced into ES cells by oocytes by fusion cell with a yeast spheroplast [see p. 12, lines 24-35]. Kuncherlapati *et al.* teach that the host immunoglobulin loci (both heavy chain alleles and both light chain alleles (kappa and lambda) would be rendered non-functional by homologous recombination by the introduction of homologous DNA via a construct that can disrupt the target locus in embryonic stem cells [see pp. 14-15, bridging paragraph]. They further teach that a marker gene can be used in the targeting construct, such as G418 resistance [see p. 16, lines 31-36].

Note that with regard to the claimed microcell, the specification teaches that a microcell is, "a structural body in which one to several chromosomes are encapsulated with a nuclear membrane and a plasma membrane." [See pp. 6-7, bridging paragraph]. Accordingly, the YAC containing yeast spheroplast as taught by Kuncherlapati is encompassed by the specification's definition of microcell.

Accordingly, Kuncherlapati *et al.* anticipate the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1-23, 25, 84, 86-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tomizuka *et al.* [**Nat. Gen.**, 16:133-143, 1997] when taken with Hadlaczky *et al.* [**US Pat. No. 6,025,155**, filed August 7, 1996].

Tomizuka teach the introduction of human chromosome or chromosome fragments into mouse ES cells by microcell-mediated chromosome transfer [MMCT]. In particular, Tomizuka teach the introduction of chromosomes (or chromosome derived fragments) which carry the genes for human antibodies from unrearranged human Ig genes [Ig heavy, λ or κ genes], which are found on human chromosomes 2, 14 and 22, into mouse ES cells. In particular, whole cell fusion of human primary fibroblasts with mouse A9 ES cells was performed, and the resulting hybrid cells were screened by PCR and FISH [see p. 133-134 and Figure 1]. It was found that intact human chromosomes 14 and 22 were identified in hybrids A9/14-C11 and A9/22-G2. These cells were then injected into 8-cell stage embryos and produced chimeric mice [see p. 137, 2nd column]. Tomizuka state that this demonstration would allow for the generation of mice containing any desired human chromosome

or fragments derived from a specific chromosomal region [see p. 140, col. 1, 2nd paragraph, lines 7-14]. Tomizuka teach that using the Cre-loxP system to replace specific mouse chromosomal regions with the corresponding human chromosomal fragment in the microcell-hybrid ES cells [see p. 140, 2nd column, 2nd full paragraph, lines 4-7]. Tomizuka differ from the claimed invention in that they do not teach or suggest introducing a foreign chromosome into a chicken DT-40 cell.

However, prior to the time of the claimed invention, Hadlaczky teach mammalian artificial chromosomes [MACS] and artificial chromosomes from higher eukaryotic species such as insects, birds and fowl which are used in methods for preparing cell lines that contain artificial chromosomes. Hadlaczky teach that chromosomes can be transferred by preparing microcells containing an artificial chromosome and then fusing them with selected target cells, for example, microcell fusion of an artificial chromosome into the chicken DT-40 cells [see col. 21, lines 8-18].

Accordingly, in view of the combined teachings of Tomizuka and Hadlaczky, it would have been obvious for one skilled in the art to modify the method of Tomizuka for producing cells comprising modified foreign chromosomes by microcell fusion followed by homologous recombination using a cell such as the chicken DT-40 cell. One of skill in the art would have been sufficiently motivated to make such a modification, as asserted by Hadlaczky, that DT-40 cells could be used in microcell fusion to introduce artificial chromosomes into avian cells [see col. 21, lines 14-18].

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear and convincing evidence to the contrary.

Claims 1-19, 21-25 and 84, 86-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tomizuka *et al.* [**Nat. Gen.**, 16:133-143, 1997] when taken with Gerdes [**FEBS** 389:44-47, 1996].

Tomizuka are described *supra*. They differ from the claimed invention in that they do not teach that the marker gene that is used for screening the cells comprising foreign chromosomes is a green fluorescent protein [GFP] encoding gene. However, prior to the time of the claimed invention, Gerdes teaches GFP and its applications in cell biology, such as a reporter for gene expression, a marker to study cell lineage, and as a tag to localize proteins in living cells [see p. 44, 1st column, *Introduction*, lines 20-23].

Accordingly, in view of the combined teachings of Tomizuka and Gerdes, it would have been obvious for one skilled in the art to modify the methods for producing cells comprising modified foreign chromosomes by microcell fusion followed by homologous recombination by using a marker such as GFP. One of ordinary skill would have been sufficiently motivated to make such a modification because, as asserted by Gerdes, GFP is useful as a reporter for gene expression.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear and convincing evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to Patsy Zimmerman, Patent Analyst, at (703) 305-2758. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703)872-9306.

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